

August 8, 1973

Mr. Fred H. Holt
Animal Health Institute
1030 15th Street, N.W.
Washington, D.C. 20005

Dear Mr. Holt,

Thank you for your interesting communication of August 1st.

As you may already know from some of my public statements, I am fully sympathetic with your scientific criticisms of the Delaney Amendment. In practice I am not sure that it has been applied as blindly as the letter of the law would allow for. In fact, Mr. Peter Hut, Chief Counsel for the FDA, has pointed out that almost all of the regulatory actions that have been popularly associated with the "Delaney Clause" have in fact been promogated under the mandate of the general safety requirement.

This is not to sweep away the problem of potential abuse and public loss from an indiscriminating application of the Delaney Clause.

However, I cannot agree with some of the basic philosophy of your report, as it would seem to me still incumbent on the introducer of a new product to verify its safety, not in absolute terms necessarily, but at least to a level which is commensurate with the estimated risk. The very first recommendations suggest that "judgement withheld until the data are confirmed"; but the problem is then what is the appropriate public policy action during a period of suspended judgement?

For these reasons I have argued against the direct extension of the principles of the Delaney Clause to situations like mutagenesis and teratology. Instead I am inclined to support Senator Nelson's version which would allow prima facie evidence of public harm to be overridden by a judgement by the secretary that the probable public benefit exceeds the public risk. I would also be prepared to support the extension of such language to cancer risk as well, for I agree with you that there are inherent paradoxes in the strict application of the Delaney language. I do not believe that such decisions about the broader values of permission versus restriction should be allowed to occur by default, even in the absence of the information that one would like to have to make a secure scientific judgement.

I must take very specific exception to the concluding remarks on page 11 which attack the principle of the use of exaggerated doses. Of course, I accept the possibility, even the likelihood, that the use of such levels of dose may sometimes distort the appropriate model of drug metabolism in the human exposed at typical levels. I would agree

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that conclusions that have been reached by the use of exaggerated doses should be rebuttable by explicit evidence that warrants the influence that they have distorted the experimental finding. But to abolish the use of exaggerated doses in chronic toxicity experiments would create more problems than it solves, for in many situations it will be simply impractical to study a sufficiently large population to make precise estimates of low-level risks. Where very large numbers are exposed in commercial practice -- as is often true for food additives -- risks at levels like 10^{-4} or 10^{-5} which are almost inaccessible to laboratory examination, would nevertheless loom very large in public policy determinations. Furthermore, exaggerated doses may give a methodology which is invaluable in exploring the possibilities of anomalous response to lower levels of a drug in isolated members of the population. We already know that there are considerable variations within the human population in the very capacity for metabolic drug detoxication which is the foundation of the threshold argument.

I am surprised that your discussion does not give more emphasis to the estimation of benefit, the level of which should certainly temper one's judgement about the level of risk-taking that might condoned.

As this is a general area of public policy comment which is unlikely to be conclusively settled in the near future, and with which I predictably may continue to be engaged, I appreciate the opportunity to discuss these matters with you and I hope you might keep me on your mailing list for further communications. If you have a copy of the federal register for July 19th conveniently accessible, I wonder if you could send me the reference you quoted in your letter.

Sincerely yours,

Joshua Lederberg
Professor of Genetics

P.S. I would be interested to have more information about the AHI generally and its activities and membership. Conversely I will not complain at all if you wish to send copies of my response to the members of the Toxicology Task Force.